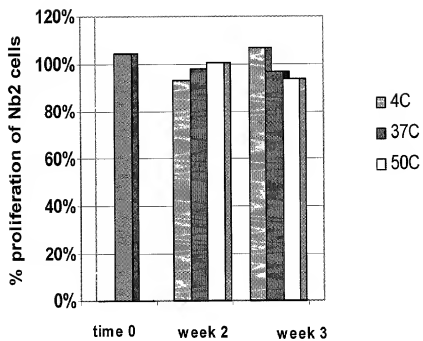
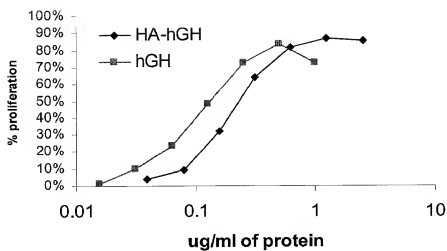


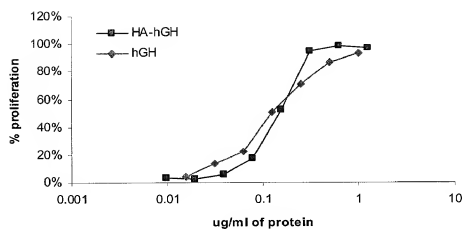
**Figure 1**



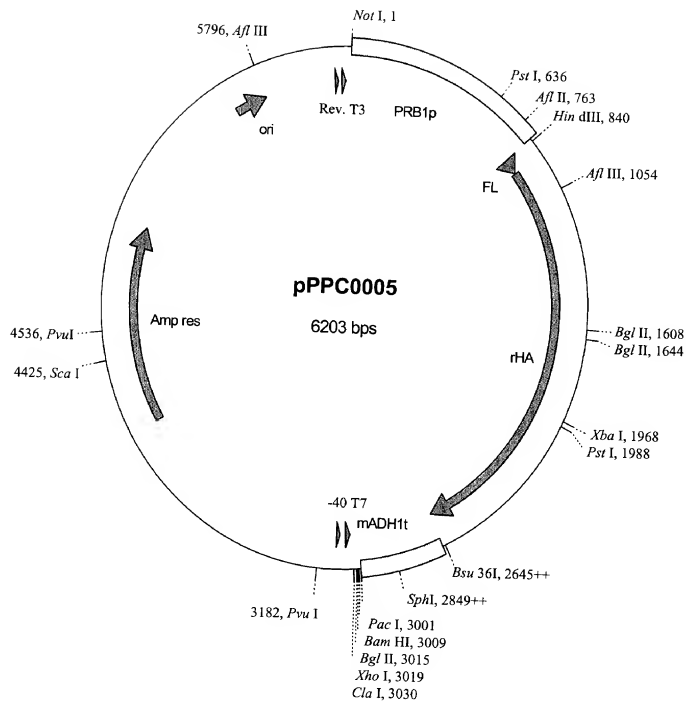
**Figure 2**



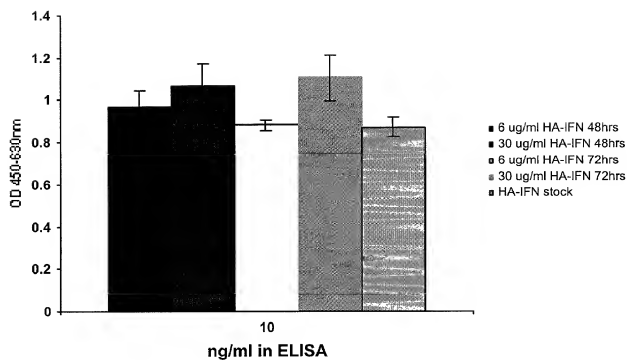
**Figure 3A**



**Figure 3B**

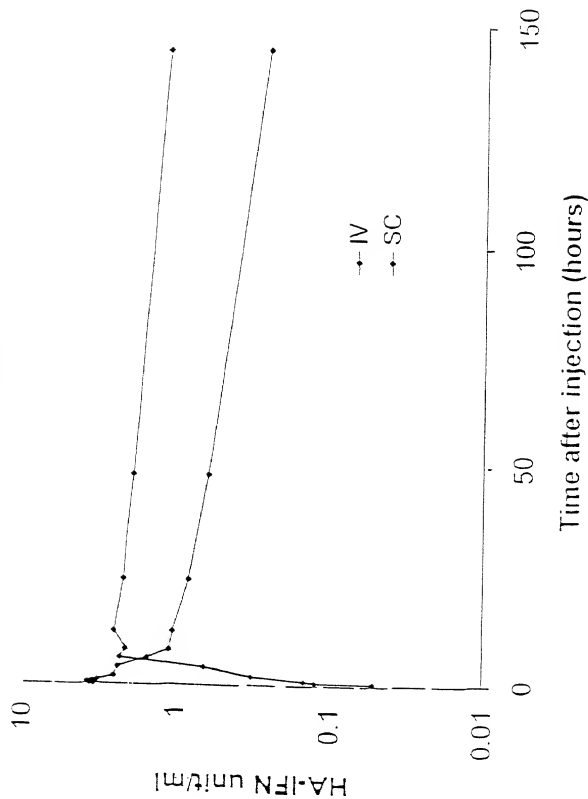


**Figure 4**

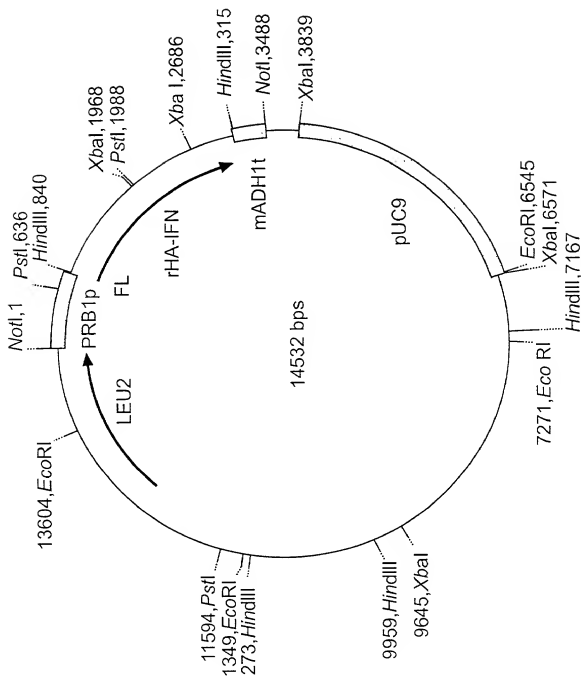


**Figure 5**

Figure 6







**FIG. 8**

# Figure 9

1	DAHKSEVAHR	FKDLGEENFK	ALVLIAFAQY	LQQCPFEDHV	KLVNEVTEFA
	HHHHH	HHH	HHH	HHHHHHHHHH	HHHHH
	<b>I</b>		<b>II</b>		<b>III</b>
51	KTCV <b>ADESAE</b>	NCDKSLHTLF	GDKLCT <b>TVATL</b>	RET <b>Y</b> EGMADC	CA <b>KOE</b> PERNE
	HHHHH	HHHHH	HHHHH	HHHH	H
101	CFLQHKDDNP	NLPRLVRPEV	DVMCTAFHDN	EETFLKKYLY	EIARRHPYFY
	HHHH	H	HHHHHHHH	HHHHHHHHHH	HHHHH
	<b>IV</b>				
151	APELLFFAKR	YKAA <b>FT</b> CCO	<b>AADKAA</b> CLLP	KLDELRDGK	ASSAKQRLKC
	HHHHHHHHHH	HHHHHHHHHH	HHHHH	HHHHHHHHHH	HHHHHHHHHH
	<b>V</b>				
201	ASLQKFGERA	FKAWAVARLS	QRFPKAEFAE	VSKLVTDLTK	VHTECC <b>HGD</b> L
	HHHHH	HH	HHHHHHHHHH	HH	HHH
	<b>VI</b>		<b>VII</b>		
251	LECA <b>DD</b> RADL	AKYIC <b>EN</b> ODS	<b>ISSK</b> LKECCE	KPLLEKSHCI	AEVENDEMPA
	HHHHHHHHHH	HHHHH	HHHHH	HHHHHHH	H
301	DLPSLAAD <b>F</b> V	ESKDVCKNYA	EAKD <b>VF</b> LGMF	LYEYARRHPD	YSV <b>V</b> LLRLA
	HHHH	HHHHHH	HHHHHHH	HHHHHH	HHHHHHHH
	<b>VIII</b>				
351	KTYET <b>T</b> LEKC	CA <b>AA</b> D <b>P</b> HECY	AKV <b>F</b> DEFKPL	VEEPQ <b>N</b> L <b>I</b> KQ	NCELFEQ <b>L</b> GE
	HHHHHHHHHH	HH	H	HHHHH	HHHHHHHHHH
	<b>IX</b>				
401	YKFQ <b>N</b> ALLVR	YTKK <b>V</b> PQVST	PTLVE <b>V</b> SRNL	GKVGSKCC <b>KH</b>	PEAK <b>R</b> MP <b>C</b> AE
	HHHHHHHHHH	HHHH	H	HHHHHHHHHH	HHH
	<b>X</b>		<b>XI</b>		
451	DYLS <b>V</b> LVNLQ	<b>CVL</b> HE <b>K</b> TP <b>V</b> TS	DR <b>V</b> TKC <b>C</b> TES	<b>LVN</b> RR <b>P</b> CF <b>S</b> A	LEVDE <b>T</b> Y <b>V</b> PK
	HHHHHHHHHH	HHHHH	HHHHHHHHH	HHHHHHHH	
501	EFNAET <b>F</b> TFH	ADICTLSEKE	RQIKKQ <b>T</b> ALV	ELVKHK <b>P</b> KAT	KEQLKAV <b>M</b> DD
	HHH	HHH	HHHHMM <b>E</b> HHH	HHH	HHHHHHHH
	<b>XII</b>				
551	FAAFVEK <b>C</b> CK	<b>ADD</b> K <b>E</b> T <b>C</b> FAE	EGKKLVAASQ	AALGL	
	HHHHHHHH	HHHH	HHHHHHHHHH	HH	

## Loop

I	Val54-Asn61
II	Thr76-Asp89
III	Ala92-Glu100
IV	Gln170-Ala176
V	His247-Glu252
VI	Glu266-Glu277

## Loop

VII	Glu280-His288
VIII	Ala362-Glu368
IX	Lys439-Pro447
X	Val462-Lys475
XI	Thr478-Pro486
XII	Lys560-Thr566

# Figure 10

## a. Randomisation of Loop IV.

IV  
 151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDELRLDEGK ASSAKQRLKC  
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHH HHHHHHHHHH

IV  
 151 APELLFFAKR YKAAFTECCX XXXXXXCLLP KLDELRLDEGK ASSAKQRLKC  
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHH HHHHHHHHHH

X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

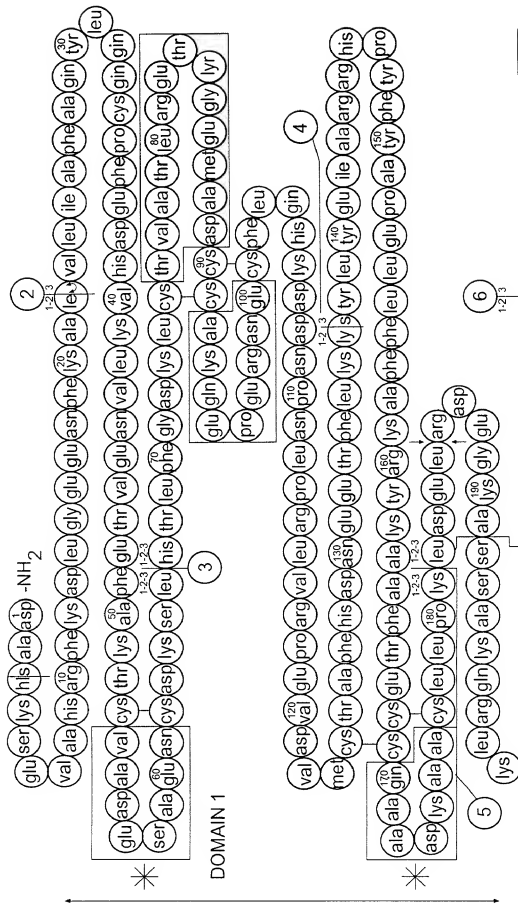
## b. Insertion (or replacement) of Randomised sequence into Loop IV.

$(X)_n$



IV  
 151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDELRLDEGK ASSAKQRLKC  
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHH HHHHHHHHHH

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.



TO FIG. 11B

TO FIG. 11B

FIG. 11A

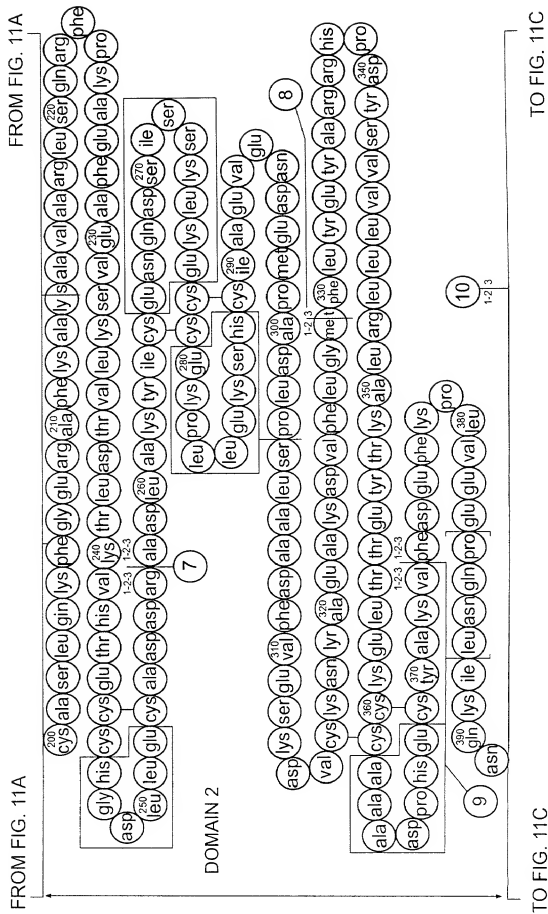
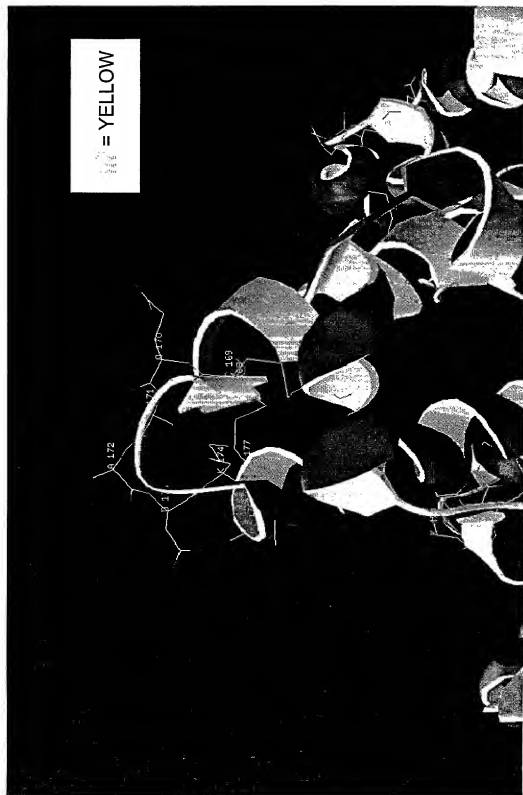


FIG. 11B

FROM FIG. 11B

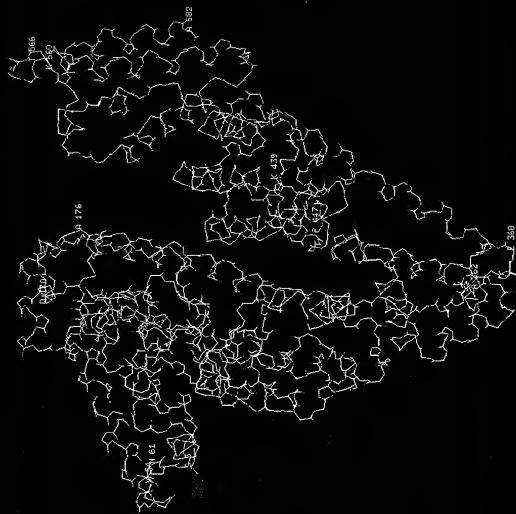


**FIG. 11C**

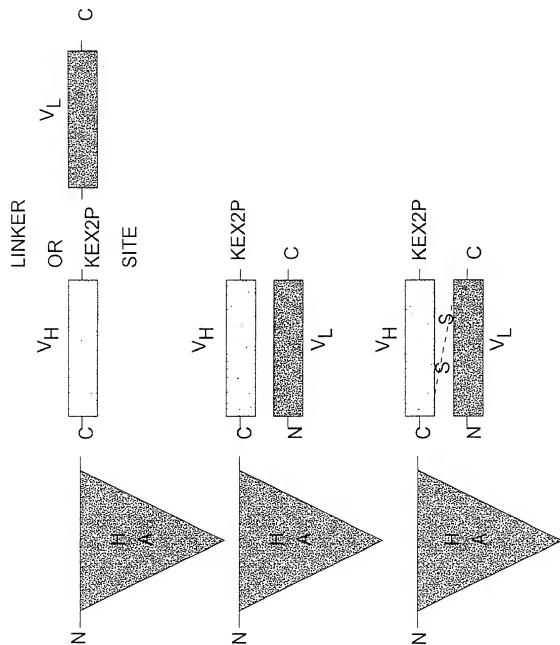


DISULFIDE BONDS SHOWN IN YELLOW

**FIG. 12:**  
LOOP IV GLU170-A176



**FIG. 13**  
TERTIARY STRUCTURE OF HA



**FIG. 14**

1 CAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA AAT TTC AAA 60  
 1 D A H K S E V A H R F K D L G E E N F K 20

61 GCC TTG GTG TTG ATT GGC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120  
 21 A L V L I A F A Q Y L Q Q C P F E D H V 40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180  
 41 K L V N E V T E F A K T C V A D E S A E 60

181 AAT TGT GAC AAA TCA CTT CMT ACC CTT TTT GGA GAC AAA TTA TSC ACA GTT GCA ACT CTT 240  
 61 N C D K S L H T L F G D K L C T V A T L 80

241 GGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300  
 81 R E T Y G E M A D C C A K Q E P E R N E 100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360  
 101 C F L Q H K D D N P N L P R L V R P E V 120

361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420  
 121 D V M C T A F H D N E T F L K K Y L Y 140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480  
 141 E I A R R H P Y F Y A P E L L F F A K R 160

Figure 15A

481 TAT AAA GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC CTG CTG TTG CCA 540  
161 Y K A A F T E C C Q A A D K A A C L L P 180

541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC ABA CAG AGA CTC AAA TGT 600  
181 K L D E L R D E G K A S S A K Q R L K C 200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660  
201 A S L Q K F G E R A F K A W A V A R L S 220

661 CAG AGA TTT CCC AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720  
221 Q R F P K A E F A E V S K L V T D L T K 240

721 GTC CAC ACG ACG GAA TGC TGC CAT GCA GAT CTG CTT GAA TGT GCT GAT GAC AGG GCG GAC CTT 780  
241 V H T E C C H G D L L E C A D D R A D L 260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840  
261 A K Y I C E N Q D S I S S K L K E C C E 280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900  
281 K P L L E K S H C I A E V E N D E M P A 300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960  
301 D L P S L A A D F V E S K D V C K N Y A 320

Figure 15B

961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020  
321 E A K D V F L G M F L Y E Y A R R H P D 340

1021 TAC TCT GTC CTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080  
341 Y S V V L L L R L A K T Y E T L E K C 360

1081 TGT GGC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140  
361 C A A A D P H E C Y A K V F D E F K P L 380

1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200  
381 V E P Q N L I K Q N C E L F E Q L G E 400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260  
401 Y K F Q N A L L V R Y T K K V P Q V S T 420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320  
421 P T L V E V S R N L G K V G S K C C K H 440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG CTC CAG AAC CAG TTA 1380  
441 P E A K R M P C A E D Y L S V V L N Q L 460

1381 TGT GTG TTG CAT GAG AAA AGG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440  
461 C V L H E K T P V S D R V T K C C T E S 480

Figure 15C

1441 TTG GTG AGC AGG CGA CCA TGC TTT TCA GCT CTG GAA CTC GAT GAA ACA TAC GTT CCC AAA 1500  
 481 L V N R R P C F S A L E V D E T Y V P K 500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560  
 501 E F N A E T F T F H A D I C T L S E K E 520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAG AAG CCC AAG GCA ACA 1620  
 521 R Q I K K Q T A L V E L V K H K P K A T 540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680  
 541 K E Q L K A V M D D F A A F V E K C C K 560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GCT GCA AGT CAA 1740  
 561 A D D K E T C F A E E G K K L V A A S Q 580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782  
 581 A A L G L \* 585

**Figure 15D**